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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,752	01/11/2001	Johannes Jacobus Voorberg	294-86	5298

7590 11/02/2005

Ronald J Baron
Hoffmann & Baron
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,752	VOORBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-59,67,68,70-73,76-80 and 82-87* is/are pending in the application.

4a) Of the above claim(s) *19,21-59,80 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-18, 20, 67-68, 70-73, 76-79 and 85-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 17-59, 67-68, 70-73, 76-80 and 82-87 are pending.

2. Claims 19, 21-59, 80 and 82-84 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

3. Claims 17-18, 20, 67-68, 70-73, 76-79 and 85-87 are under examination as they read on a polypeptide capable of specific bindign to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable region of the heavy chain of a human antibody with factor VIII specificity or parts thereof which at least includes the CDR3 region and a pharmaceutical composition thereof and DP-10 as the species.

4. In view of the amendment filed on 9/6/05, only the following rejections are remained.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 17, 18, 70-73, 76-79 and 85-86 stand rejected under 35 U.S.C. 102(b) as being anticipated by Davies (Davies et al 1997, thromb. Haemostas. Supplement: 2352) for the same reasons set forth in the previous Office Action mailed 3/11/05.

7. The declaration by Dr. Voorberg under 37 CFR 1.132 filed 9/6/05 is insufficient to overcome the rejection of claims 17, 18, 70-73, 76-79 and 85-86 based upon 35 U.S.C. § 102(b) as being anticipated by Davies as set forth in the last Office action because none of the twelve different scFvs tested in table 1 came from the reference relied upon, Davies et al reference. It is noted that it is applicant's burden to show that the reference scFvs do not interference with the activity of factor VIII inhibitors recited in the claims. In the instant case, Applicant tested scFvs which are not taught by Davies' reference.

Applicant's arguments, filed 9/6/05, have been fully considered, but have not been found convincing.

Applicant argues that the claimed polypeptides bind to FVIII and interfere with the activity of FVIII inhibitors. However, Davies et al is completely silent about whether the scFvs are capable of interfering with the activity of FVIII inhibitors. Applicant submits that scFvs that specifically bind FVIII and interfere with the activity of FVIII inhibitors is neither disclosed or suggested, nor an inherent property of the scFvs of Davies et al. Davies et al examined the Ig variable domain structure of immune FVIII antibodies obtained by Vgene phase display technology form

haemophilia A patient high peak inhibitor levels. Applicant contends that the expectation of any skilled person is that the approach of Davies et al. would yield scFvs which strongly inhibit FVIII. Applicant points out that the present invention is the novel and surprising discovery of scFvs that specifically bind FVIII and interfere with the activity of FVII inhibitors.

Again, when a claim recites using an old composition or structure (e.g. a polypeptide capable of specific binding to factor VIII comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody) and the use is directed to a result or property of that composition or structure (interference with the activity of factor VIII inhibitors), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant points out that the claimed polypeptides typically use different VH segments than those of the scFvs disclosed in Davies et al. Further applicant points that the VH segments used in the claimed polypeptides include C2 domain (DP10, DP14, DP88), A3-C1 domain (DP15, DP31, DP49, DP77, and A2 domain (DP10, DP47). However, the VH segments used in the scFvs of Davies are V3-15+, DP38, DP54, DP73, DP74. Applicant argues that the differences in the VH segments used in the claimed polypeptides and those used in the scFvs of Davies et al make it unlikely that the scFvs described in Davies et al possess the claimed features of (i) specific binding to FVIII and (ii) interference with FVIII inhibitors. Applicant concludes that chemical compositions that are not the same are expected not to have the same property.

However, the Examiner notes that both the referenced VH segments and the claimed VH segments bind to the same A2 domain and the light chain (A3-C1-C2), the resultant VH segment DP10, DP14, DP88, DP15, etc. is an inherent property. Further, an antibody property is determined by (i) its CDRs and (ii) the epitope it binds, irrespective of the VH segment it derived from. For example, humanized antibodies would have at least the CDRs of a murine mAb drafted into a human framework, the resultant antibodies would have the same binding epitope specificity as the murine mAb. The structure of the humanized antibodies would be at least 90% different that the structure of the murine mAb, however both the humanized and the mAb antibodies would have the same epitope binding specificity.

Applicant argues that not all svFvs that bind FVIII are capable of interference with FVIII inhibitors. Applicant points to Dr. Voorber Declaration to establish that not all scFvs that bind FVIII are capable of interference with FVIII inhibitors. Applicant concludes that interference with FVIII inhibitors is not an inherent property of all scFvs that bind FVIII. Applicant points that the examiner is incorrect to conclude that the ability to interfere with FVIII inhibitors is an inherent property of the scFvs of Davies et al.

However, when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP Section 716.07.

Applicant argues that Davies does not provide an enabling disclosure. Applicant submits that there is no indication that the scFvs of Davies et al were deposited with any depository institution to provide access to the public. Applicant concludes that the public is not in possession of the eight scFvs disclosed in Davies. Applicant further argues that the disclosure of Davies is not described in a way which would have allowed one skilled in the art to make the scFvs disclosed. Moreover, the disclosure of Davies is not sufficient to fully characterize the structure of the scFvs. Applicant concludes that Davies' disclosure is not enabling.

While applicant implies that the meaning of "public was in possession" to be limited to a deposit of the scFvs in a depository institution to provide access to the publich, however, the examiner notes that publications, patents, public uses and sales are defines the public was in possession". In this instant case, Davies publication is indicates that the public is in possession of the claimed scFvs at least one year prior to the claimed invention. Regarding the issue that Davies disclosure is not described in a way which could have allowed one skilled in the art to make the scFvs disclosed, the Examiner notes that Davies taught a method of selecting by panning rFVIII for using V gene phage display technology from 3 heamophilia A patients with peak inhibitor levels above 60 Bu/ml to obtain the scFvs.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 20 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of U.S Patent No. 4,731,245 (of record) for the same reasons set forth in the previous Office Action mailed 3/11/05.

Applicant's arguments, filed 9/6/05, have been fully considered, but have not been found convincing.

Applicant traverses the rejection on the ground that there is no disclosure or suggestion in Davies et al of polypeptides that bind to FVIII and interfere with the activity of FVIII inhibitors. Applicant submits that claim 20 is patentable over Davies at least for the same reasons that claims 17 and 18 are patentable.

However, the Examiner's position is the same as indicated under 35 U.S.C 102(b) rejection. Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody fragments taught by Davies et al in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent to enable the administration of the antibody at a daily dose as taught by the `245 patent.

10. Claims 17 and 67-68 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of Foung et al 1986 and U.S Pat. No. 5,916,771 for the same reasons set forth in the previous Office Action mailed 3/11/05.

Applicant's arguments, filed 9/6/05, have been fully considered, but have not been found convincing.

Applicant traverses the rejection on the ground that nowhere in Davies is there any disclosure or suggestion of a polypeptide that is capable of binding to FVIII and interferes with the activity of FVIII inhibitors. Further, the secondary references, namely Foung et al and the `771 patent, also do not disclose or suggest such polypeptide. Applicant contends that the rejection of the claism is improper in the absence of such a disclosure or suggestion. Applicant concludes that the claimed invention cannot be considered obvious over Davies in view of Foung and the `771 patent.

However, the Examiner's position is the same as indicated under 35 U.S.C 102(b) rejection. Further, given that haemophilia A is an autoimmune blood disorder, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate human monoclonal antibodies as taught by Foung et al with subclass IGG4 as taught by the `771 patent using the target B cell epitopes localized on the A2 and C2 domains from a haemophilia A patients with peak inhibitory levels above 60 Bu/ml as taught by Davies et al because IgG4 exhibit no cellular cytotoxicity or complement fixation in treating autoimmune diseases as taught by the `771 patent. Further, because human monoclonal antibodies are important factors in facilitating wider clinical applications as taught by the Foung et al.

11. The following new ground of rejection is necessitated by the amendment submitted 9/6/05.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 87 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that specifically binds factor VIII, antibodies derivatives of svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO: 23), scFv-IT-2 (DP-14), CHIT2 (SEQ ID NO: 25), VH-IT2 (SEQ ID NO: 25, VH EL-5 (DP-14) (SEQ ID NO: 27) and VH EL-25 (DP-14) SEQ ID NO: 28 that bind C2-domain of factor VIII light chain, B38 (SEQ ID NO: 32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO: 36), B04 (SEQ ID NO: 38) that bind A3-C1 domain of factor VIII light chain for the diagnostic assay does not reasonably provide **enablement** for an isolated polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, wherein the polypeptide comprises theheavy chain variable region comprises SEQ ID NOS: 24(DP10), 26(DP14), 31 (DP15), 33(DP31), 35 (DP49), 37 (DP77), 52 (DP47) and any "light chain variable region of a human antibody". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a polypeptide having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. The specification provides no direction or guidance regarding how to produce such polypeptides as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional polypeptide antibody can be obtained by the heavy chain variable region comprises SEQ ID NO: 24, 26, 31, 33, 35, 37 or 52 and any "light chain variable region of a human antibody".

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this

final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
October 20, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600